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Estimation of pooled reference values for cadmium in blood using meta-analysis and TRACY criteria

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Abstract

Reference values for blood-cadmium levels (B-Cd) are available for only a limited number of geographical areas and for particular population strata (sex, age, smoking habits). This paper, in agreement with the TRACY guidelines, describes and discusses the criteria used to rank published papers on reference values for cadmium retrieved by Medline and Toxline between 1976 and 1991. The TRACY criteria deal with the grading of published papers in terms of their suitability for calculating provisional reference values. Only four out of 18 papers were considered suitable for the TRACY project. The four articles were finally used via meta-analysis to provide provisional reference values for smokers and non-smokers. The comparison of results obtained using published statistics and individual data is used to discuss the appropriateness of meta-analysis in the case of cadmium. Due to the availability of large enough studies and to the clear differences across countries, the suitability of a compound upper reference limit to B-Cd levels seems limited.

Keywords: Biological indicators; Blood cadmium; General population; Reference values; Meta-analysis; Pooled estimates

1. Introduction

Reference values define levels of biological indicators in the general population not occupationally (environmentally) exposed to the toxic substance under study. It is necessary to refer to these values in order to compare data obtained through biological monitoring programmes in a population which is presumed to be exposed, either for occupational or environmental reasons. The term reference values replaces the old concept of 'normal values' [1]. In this report, an attempt is made to establish reference values for blood-cadmium (B-Cd) levels retrieved from published material. In planning this study we took into account the work already done on this topic by the TRACY project committee [2], which repre-

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sents an attempt to coordinate quality criteria being developed by the ICOH Scientific Committee on Toxicology of Metals and by the IUPAC Commission on Toxicology.

In particular, we applied a revised version of the framework used in the paper 'A review of normal concentrations of mercury in human blood' by Brune et al. published in 1991 [3]. From this study, we took both the definition of reference values and the principal criteria for grading published papers.

According to Brune et al. [3] reference values may be defined as follows: 'concentration interval of an element in samples from a defined part of a human soft or hard tissue or from a body fluid randomly selected from a sufficient number of healthy individuals living in a defined geographical area with defined life style and eating, drinking and smoking habits, with defined age and sex, not being professionally exposed to the appropriate element'.

This general definition, however, if followed literally will lead to the conclusion that meta-analysis is not applicable in this context since it explicitly refers to geographically specific reference values. Nonetheless, it has to be considered that not all the mentioned factors (geographical area, personal life style, sex, age, etc.) affect the levels of the metal under study. As a consequence, a wider definition could be adopted which considers healthy individuals, not occupationally exposed who are homogeneous for the 'relevant' factors, without any further specification.

The main criteria, established by the TRACY committee in the attempt to derive reference values via published statistics, provide critical evaluation of sampling conditions and of analytical treatment (Table 1). These criteria may be broadly used for all metals. However, for the sampling conditions in particular, it is necessary to adopt specific variables for each metal considered.

This paper is divided into two parts: Part 1 summarizes and completes the preliminary results presented at the International Symposium 'Cadmium in the Human Environment: Toxicity and Carcinogenicity' [4]. This part, in agreement with the TRACY guidelines, describes and discusses the criteria (Table 2) used to rank published papers on reference values for cadmium retrieved by Medline and Toxline from 1976 to 1991.

Table 1
Criteria used for quality grading of publications on B-Cd

Sampling (S)	
S1	S2
Number of subjects	Age
Statistical selection criteria	Sex
	Smoking habits
	Collection of biological samples
	Alcohol consumption
	Dietary habits
	Indirect exposure
	Residence
	Country
Analysis (A)	
A1	A2
Analytical method	Statistical distribution
Use of appropriate reference material	Appropriate parameter estimation
Detection limits, precision, bias	
Assessment with two or more different methods	

Since this study was planned before the TRACY guidelines were completed, not all the phases described in Table 2 were fulfilled. Furthermore, we employed four evaluators, two occupational physicians and two medical statisticians. As a result, the statistical methods used to obtain a pooled estimate of the upper reference limit for

Table 2
Proposed TRACY evaluation phases

No.	Description
1	Pilot studies made by two evaluators
2	Reading + evaluation made by the evaluators
3	Consensus among evaluators
4	Evaluations reviewed by TRACY-group
5	Evaluators finalize a report
6	Report open for review by referees
7	Published report that may be updated in a data base

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blood-cadmium are presented in detail. The final subsection of this part presents the results and discusses the opportunity to provide an overall estimate of reference limits.

Part II is based on individual records rather than on published results, which are presented as summary statistics. The availability of Italian and British data on individual blood samples is used to explore the influence of different personal habits (alcohol consumption, smoking habits) and demographic variables (age, sex, place of residence) on B-Cd levels. The results of this analysis are used to discuss the limits of meta-analytic studies in the context of reference values for heavy metals.

2. PART I

2.1. Evaluation of published information

To evaluate information published on B-Cd reference values, we reviewed articles published in the international literature between 1976 and 1991. Papers were retrieved by Medline and Toxline. It was surprising that for a metal which has been extensively studied from a toxicological viewpoint, the number of studies regarding reference values was rather small. In fact, we found only 18 publications.

To assess the quality of these 18 articles on B-Cd, quality grading was carried out by considering sampling conditions as well as pre-analytical, analytical and statistical treatments (Table 1). The evaluation was performed independently by four evaluators: two occupational physicians and two medical statisticians, so as to cover all the relevant aspects listed in Table 1. This phase was followed by a consensus meeting between evaluators and the grading was then settled on the basis of the agreement reached, using the 'stars' grading system proposed by the TRACY group (Table 4).

Table 3
Main variables to be considered in sampling subjects for B-Cd

Variable	Weighting
Age	+
Sex	+
Alcohol	–
Smoking	+ + +
Dietary habits	+ + +
Indirect occupational exposure (e.g. white collars)	+ +
Residence (rural, industrial area)	+
Medication	– +
Hobbies	+
Country	+ + +

2.1.1. Sampling

Papers were ranked on the basis of sample size, statistical selection criteria (S1) and sampling conditions (S2). The latter included considerations on contamination and losses in the process of sample collection (e.g. needles, vials, etc.). We considered adequate those studies based on a number of subjects greater than 10 per stratum. The rationale of this decision was to guarantee a homogeneous quality standard of papers, in a situation where studies of large dimension were present. As for S2, since the criteria necessary to evaluate the sampling conditions must be specific to the metal under study, we made a list of variables whose importance has been documented and/or presumed in the literature or in our personal experience, i.e.: age, sex, smoking habits, alcohol consumption, dietary habits, indirect exposure to metals, residence in a urban or rural area, country [5–9]. In Table 3, we propose a weighting system for the effect of each variable on B-Cd levels.

2.1.2. Analysis

In order to attribute a quality grading to analytical treatment, (A1) we used the criteria pub-

Table 4
Distribution of quality scores for 18 publications on B-Cd

Quality score	Sampling		Analysis	
	S1	S2	A1	A2
Excellent (***)	16	6	2	5
Good quality (**)		4	3	0
Acceptable (*)		2	2	8
Unsuitable for TRACY	2	6	11	5

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lished by Brune et al. [3]: analytical method, use of reference, accuracy/precision/sensitivity, assessment with two or more different methods. On the other hand, the main criteria used for evaluating the appropriateness of the statistical treatment (A2) were: (1) reference to the statistical evaluation of intra/inter laboratory quality control; (2) methods for sampling individuals from the reference population; (3) data description and dredging; (4) reference to the log-normal distribution; (5) availability of the relevant measures of central tendency and dispersion, geometric mean (G.M.) and geometric standard deviation (G.S.D.); (6) stratification for known confounders, such as smoking habits and country of residence.

As a result, the approach described in this paper differs from that adopted by Brune et al. [3], since they assumed that mercury blood levels were normally rather than log-normally distributed. A detailed discussion of the consequences of these two approaches has been presented elsewhere [4].

2.1.3. Results of grading

The 18 papers on B-Cd, which dealt with 16 400 subjects, were graded according to the classification summarized in Table 4. The number of papers considered in the subsequent study was reduced to four, comprising 2290 subjects [10–13]. A study [17] of 2009 subjects was evaluated separately because its results clearly differed from the estimates provided by all the other papers.

In a few circumstances, we were forced to exclude papers only because the authors did not provide the statistics necessary for our purposes [14–17]. However, these studies received a high grading as regards as S1, S2 and A1.

2.2. Statistical methods

In order to define reference values for blood-cadmium, we assumed that the distribution of the original values was a log-normal density function. Only the papers, reporting the geometric mean (G.M.) and the geometric standard deviation (G.S.D.) and which received an adequate grading, were considered in our analysis.

Pooled estimates of the G.M. and the G.S.D. were derived using the formulas:

$$GM_{pool} = exp\left[\frac{\sum_i n_i ln(GM_i)}{\sum_i n_i}\right]$$

$$GSD_{pool} = exp\left[\sqrt{\frac{\sum_i (n_i - 1)[ln(GSD_i)]^2}{\sum_i (n_i - 1)}}\right]$$

Since for xenobiotic substances there is no need to calculate bidirectional intervals, a unidirectional reference limit was computed. The choice of which statistical interval to compute is determined by the problem at hand. In this case, we wanted an interval to include a specified proportion p of the entire sampled population. This requirement leads to the concept of 'tolerance' interval which can be defined as that interval including at least a proportion p of the reference population at a predefined confidence level $(1 - \alpha)$ [18]. The multiplicative factor for the upper bound tolerance interval takes the following form:

$$c_{(p,1-\alpha)} = \frac{z_p + z_{(1-\alpha)}\sqrt{\frac{1}{n}\left(1 - \frac{z^2_{(1-\alpha)}}{2(n-1)}\right) + \frac{z_p^2}{2(n-1)}}}{1 - \frac{z^2_{(1-\alpha)}}{2(n-1)}}$$

where n is the sample size, and z corresponds to the Standard Normal Deviate. The subscripts p and $(1 - \alpha)$ represent the proportion of the population enclosed by the tolerance limits (0.75, 0.90) and the confidence level (0.95), respectively. The upper tolerance limit was then obtained applying the formula:

$$exp\{lnGM_{pool} + c_{(p,1-\alpha)} lnGSD_{pool}\}$$

In the case of variances heterogeneity, the calculation of pooled estimates is meaningless. Consequently, Bartlett's test was used to evaluate the variances homogeneity.

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2.3. Results and discussion

The selected papers provided enough information only on smoking habits and area of origin of subjects, which enabled us to subdivide the sample according to those variables (Table 5). The differences in G.M. between smokers and non-smokers are striking in all countries except India. The same G.M. value for smokers and non-smokers in this country has no clear explanation but could be due to differences in tobacco blend or to particular smoking habits. In fact, lower concentrations of B-Cd have been reported in cigarettes produced in Africa and in other developing areas [19]. In addition to the differences due to smoking, the variability in G.M.s across countries is evident and it is true both for smokers and non-smokers.

Table 5 does not include the studies by Watanabe et al. (1983) [13] from many Japanese regions, since the B-Cd values measured in those populations were clearly heterogeneous in comparison with those found in all the other countries. The comparison between the result published in this paper and the estimates obtained by pooling all the G.M. and G.S.D. reported in Table 5 (General caselist) is presented in Table 6. It is worth noticing two facts: first of all, the differences in G.M.s between Japanese and non-Japanese studies are considerable both in smokers and non-smokers. This difference may be mainly attributable to dietary habits and in particular to the intake of rice. Secondly, the increase in blood-cadmium levels due to smoking seems to be independent of the background level since the difference between G.M.s for smokers and non-smokers are similar in the General and the Japanese caselists.

The results of this first part of the investigation have led us to the following considerations: (a) The number of studies on B-Cd levels in the general population was rather modest and only a few of them proved acceptable by quality grading. In fact, these studies were mainly concerned with the formation of control groups for toxicological and epidemiological investigations. (b) Between-countries variability within non-smokers was very high. In fact, the average blood-cadmium levels for non-smokers in different areas ranged from 0.19 (Stockholm) to 1.06 (Tokyo). Although less pronounced, the variability in G.M.s across countries (0.92–2.81) is evident also for smokers. (c) The observed differences between non-smokers living in different geographical areas represent the contribution of environmental as well as personal habits (i.e. diet). In smokers, the effect of smoking is additional to these factors. Differences in cadmium content of tobacco and in smoking habits and intensity influence B-Cd values and contributes to geographical variation among

Table 5
Comparison of G.M.s and G.S.D.s for B-Cd levels ($\mu g/l$) in different case-lists

Country	Authors	Non-Smokers			Smokers		
		N	G.M.	G.S.D.	*N*	G.M.	G.S.D.
Belgium	Friberg and Vahter, 1983	89	0.95	1.67	44	2.13	1.92
Sweden	Friberg and Vahter, 1983	76	0.19	1.99	84	1.55	2.10
Sweden	Elinder et al., 1983	164	0.27	1.56	195	1.40	1.70
Yugoslavia	Friberg and Vahter, 1983	114	0.43	2.08	72	2.81	2.63
Israel	Friberg and Vahter, 1983	143	0.40	1.80	54	1.13	2.70
India	Friberg and Vahter, 1983	310	0.81	1.50	46	0.81	1.49
China	Friberg and Vahter, 1983	161	0.64	1.80	70	1.80	1.63
Tokyo	Friberg and Vahter, 1983	94	1.06	1.63	79	1.46	1.71
Mexico	Friberg and Vahter, 1983	47	0.30	3.30	25	2.33	2.60
USA	Friberg and Vahter, 1983	88	0.52	1.86	59	0.92	2.19
USA	Kowal et al., 1979	115	0.85	1.59	31	1.35	1.65
Peru	Friberg and Vahter, 1983	101	0.77	1.50	29	1.68	2.02

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Table 6
G.M., G.S.D., 75° and 90° centiles for cadmium levels ($\mu g/l$) by smoking habits

Group	Parameter	General caselist[a] (*N*, 2290)	Japanese caselist[b] (*N*, 2009)
Non-smokers	G.M.	0.56	3.42
	G.S.D.	1.75	1.50
	75°	0.84	4.54
	90°	1.19	5.87
	N	1502	1539
Smokers	G.M.	1.50	4.19
	G.S.D.	1.97	1.48
	75°	2.47	5.67
	90°	3.78	7.28
	N	788	470

[a]Elinder et al., 1983 [10]; Friberg and Vahter, 1983 [11]; Kowal et al., 1979 [12].
[b]Watanabe et al., 1983 [13].

smokers. (d) The inter-individual variability, as expressed by the geometric standard deviations, was homogeneous in all countries, both for non-smokers and smokers. (e) Pooled reference values can be justified on a descriptive basis and may be useful to discriminate major differences between populations. For some areas, this use of reference values appears to be of the utmost importance as confirmed by the Japanese caselist.

3. Part II

3.1. Acquisition of individual cases

To evaluate whether the results obtained by combining different estimates were coherent with those derived from individual data, we pooled subjects which were included in three Italian and one English studies.

As already mentioned, the decision to include in the meta-analysis only papers which reported G.M. and G.S.D. forced us to ignore some other studies whose sampling conditions and pre-analytical and analytical treatments were adequate. Therefore, in order to be able to re-analyze those data extensively, it was decided to contact some of the authors and ask them permission to have direct access to the individual records.

The Italian data were easy to obtain [14–16] since we have contributed to all the three studies. As for the English caselist, we contacted the authors of the study on blood-cadmium concentration in the general population of British men [17] and they kindly sent us the file containing their data.

3.2. Statistical methods

A multiple linear regression technique was employed to study the relationship between the log-transformed blood-cadmium measurements in males and age (three age classes: < 35, 35–44 and > 44 years), smoking habits (smokers vs. non-smokers and ex smokers), alcohol consumption (drinkers vs. non-drinkers), and place of residence. The most parsimonious model was obtained using a backward procedure. The *F*-test ($\alpha = 0.05$) was used as the criterion to remove non-statistically significant terms from the initial model. The SAS package was used to analyze the data set [20].

3.3. Results

The pooled analysis of Italian and British data was based on 7424 male subjects, the great majority (6919) coming from England.

As shown in Table 7, our analysis confirmed previous findings concerning the role played by smoking and geographical area. Aging was not found to influence the B-Cd concentration in the British data set, while the results of the pooled

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analysis revealed a statistically significant increment in blood-cadmium concentration moving from lower age groups to older ones. This is possibly due to the restricted age range (40–59) of the British sample. In fact, when the analysis is restricted to the Italian cases, there is an increment in the median blood-cadmium levels particularly between the first and the second age classes. Unfortunately, the pooled analysis cannot reinforce this finding since the first age class is composed of Italian subjects whose blood-cadmium levels are lower than those of the British population. Alcohol does not seem to affect the B-Cd levels.

The model containing age, smoking and place of residence explains only about 50% (P^2 = 0.56) of the total variability. The adequacy of this model in terms of goodness of fit is not very satisfactory but further information on other relevant factors (diet, environmental pollution, etc.) were not available for all subjects. It is worth mentioning that the B-Cd values vary significantly with place of residence and that the Italian levels are lower than those of the majority of the British localities.

As is evident in Table 8, the Italian values are lower, as a whole, than those of the general caselists while the British values are higher. This heterogeneity in data gathered in different geographical areas is presumably due to various levels of pollution and varying dietary habits and was already underlined when discussing the results presented in Table 5. But it has to be emphasized that such differences are true even for neighbouring areas (Milan, Brescia, Verona) formerly considered homogeneous (Table 9). Therefore, the reference values for B-Cd levels obtained through meta-analysis studies have their limitations.

4. Conclusion

In most industrialized countries, the levels of occupational hazards have been progressively decreasing and, in some cases, are approaching the levels found in the general environment. Under these circumstances, it is of utmost importance that reference values are available to: (a) Describe the actual exposure to environmental hazards in different populations. (b) Monitor the trend, over certain time periods, of the concentration of substances in biological tissues. (c) Relate the levels of biological or biomolecular markers to early toxic effects.

Meta-analysis is meaningful, particularly for obtaining the first of the listed points, when we have to deal with many studies of small dimensions (although it becomes extremely difficult to identify the sampled population) or when differ-

Table 7
Analysis of variance on log-cadmium by smoking, age, alcohol consumption and place of residence

Variable	DF	Sum of square	Mean square	*F*-value	$Pr > F$
Smoking	1	2249.971119	2249.971119	6090.38	< 0.001
Age	2	275.997265	137.998633	373.54	0.0001
Residence	26	879.077032	33.810655	91.52	< 0.001

Table 8
Comparison of B-Cd values ($\mu g/l$) between the Italian, the British and the general caselists

Caselist	*N*	Non-smokers			*N*	Smokers		
		G.M.	G.S.D.	90°		G.M.	G.S.D.	90°
Italian	835	0.37	2.08	1.01	444	0.79	1.86	1.90
English	3813	0.87	2.08	2.29	2798	2.75	1.74	5.72
General	1502	0.56	1.75	1.19	788	1.50	1.97	3.78

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Table 9
G.M.s and corresponding G.S.D.s of B-Cd (μg/l) for population samples collected in three Italian cities

Place of residence	N	G.M.	G.S.D.
Brescia	404	0.475	2.195
Verona	162	0.538	2.020
Milan	199	0.695	2.101

ent studies cover only a portion of the relevant factor's ranges (for example few studies investigate the extreme ages or the very heavy smokers, etc.). Under these circumstances, pooling is necessary to obtain estimates of sufficient precision or to provide more complete information on the effect exerted on the B-Cd levels by generally unexplored values of important factors.

In the case of cadmium, the situation is rather different since we are dealing with some large studies, big enough to provide stable estimates of the quantities of interest. In this case, the gain due to the pooling is rather negligible. In situations similar to the cadmium one, seems more relevant to study of heterogeneity and in particular the ability to identify the factors influencing it.

At present we can derive reference values which enable us to distinguish subjects living in highly polluted areas and/or with a high cadmium dietary intake from subjects with lower exposure, and in both groups we can distinguish smokers from non-smokers. It is necessary, however, to stress that reference values obtained so far cannot be utilized to discover smaller exposure differences. An improper use of these values could even conceal these rather small differences.

As underlined in paragraph 3.3 only 50% of the inter-individual variability is explained by age, smoking and place of residence. Undoubtedly, other factors such as diet, which were not considered in our model, could account for part of the unexplained heterogeneity. Nonetheless, we would like to emphasize the role of other factors on the observed variability, factors which have not been mentioned previously: the different choice of reference population and the inter-laboratory variability. None can be quantified without a planned experiment but may, in our experience, account for a large fraction of the total variability. The lack of control for these two factors may prevent the pooling of otherwise homogeneous data. In particular, the discussion concerning differences of the order of 0.2 μg/l between the various case lists should take into account the correct knowledge of the accuracy of the analytical techniques used to measure the metals.

So far, the discussion has focused on theoretical considerations concerning the possible strategies to obtain valid estimates of population reference limits. However, from a practical point of view, even if we admit that for the identification of reference values for B-Cd, it is sufficient to take into account only two variables (i.e. smoking and pollution), the question arises whether, from a toxicologic viewpoint, the rather large differences in B-Cd levels found in the studied groups are relevant. From this consideration stems the need to evaluate whether these differences are important not only for indicating the existence of different exposures but also for revealing dose levels entailing certain (toxic) effects.

In our opinion, it is necessary to verify when it is useful to pool the results of different studies and possibly to clarify the use of reference values. Furthermore, experts should discuss which B-Cd levels ought to discriminate between groups and subgroups. For example, it should be established if 0.1 μg/l B-Cd is relevant or instead if higher levels such as 0.5–1.0 μg/l are the ones to adopt. However, as a preliminary and rough guideline, we may compare the B-Cd values from one or several workers in a factory to the reference limits produced by the nearest population of those listed in Table 5. Where none of those 'reference populations' applies, pooled data in Table 8 may be used. Particular caution should be used for the reference values for smokers since the blood-cadmium concentration varies according to the number of cigarettes, the length of the cigarette, tobacco brand, etc. As an example, it has been reported that for every cigarette smoked per day, the level of B-Cd increases by 1.6% [6].

Certainly, meta-analysis studies are useful because they stimulate toxicologists and epidemiologists to apply a methodology for the formation

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of reference groups rather than to merely select 'control groups'. Meta-analysis studies have the advantage of stimulating scientists to produce better and better research on industrial and environmental toxicology.

Lastly, we must stress that the possibility of using reference values derived from meta-analysis does not mean that the laboratories in any area are exempted from producing their own reference values: these are indispensable for field investigations (and for future meta-analysis).

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